

PCT

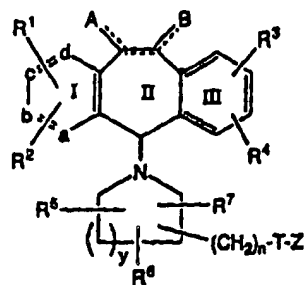
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



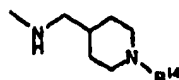
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/14, A61K 31/435, C07D 401/04		A1	(11) International Publication Number: WO 98/11097
			(43) International Publication Date: 19 March 1998 (19.03.98)
(21) International Application Number: PCT/US97/15902		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 11 September 1997 (11.09.97)		<p>Published With international search report.</p>	
(30) Priority Data: 08/713,705 13 September 1996 (13.09.96) US			
(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).			
(72) Inventors: RANE, Dinanath, F.; 2 Hayground Court, Morganville, NJ 07751 (US). COOPER, Alan, B.; 23 Natalie Drive, West Caldwell, NJ 07006 (US). MALLAMS, Alan, K.; 147 Kings Highway, Hackettstown, NJ 07840 (US). DOLL, Ronald, J.; 126 Union Avenue, Maplewood, NJ 07040 (US). NJOROGUE, F., George; 2597 Juliet Place, Union, NJ 07083 (US). TAVERAS, Arthur, G.; 43 Crestwood Road, Rockaway, NJ 07866 (US).			
(74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).			

(54) Title: SUBSTITUTED BENZOCYCLOHEPTAPYRIDINE USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE



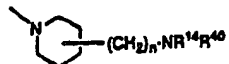
(1.0)



(I)



(II)



(III)

(57) Abstract

Novel tricyclic compounds of formula (1.0) or a pharmaceutically acceptable salt or solvate thereof, wherein: one of a, b, c and d represents N or NR⁹ wherein R⁹ is O-, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or each of a, b, c, and d are independently selected from CR¹ or CR²; each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHCO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹, -SR¹¹N(R⁷⁵)₂; y is 0 (zero) or 1; n is 0, 1, 2, 3, 4, 5 or 6; T is -CO-, -SO-, -SO₂-; or -CR³⁰R³¹; Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR⁴⁰, -SR⁴⁰, 1C-R⁴⁰R⁴², (i), (ii), -NR⁴⁰R⁴², (iii). Pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel tricyclic compound to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human.

AL

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

**SUBSTITUTED BENZOCYCLOHEPTAPYRIDINE USEFUL AS INHIBITORS OF FARNESYL-
PROTEIN TRANSFERASE****5 BACKGROUND**

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

30 SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a

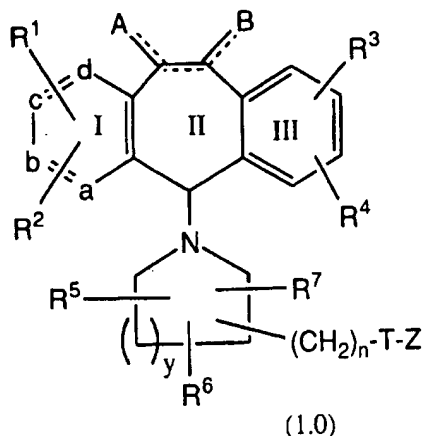
geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been

5 demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of

10 contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

15 Compounds useful in the claimed methods are represented by Formula 1.0:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or

20 -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰ (e.g., -OCH₃), -COR¹⁰, -SR¹⁰ (e.g., -SCH₃ and -SCH₂C₆H₅), -S(O)_tR¹¹

25 (wherein t is 0, 1 or 2, e.g., -SOCH₃ and -SO₂CH₃), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NH₂SO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹ (e.g., -SCH₂CO₂CH₃), -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵

is independently selected from H and -C(O)OR¹¹ (e.g.,
 -S(CH₂)₂NHC(O)O-t-butyl and -S(CH₂)₂NH₂), benzotriazol-1-yloxy,
 tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted
 tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or
 5 alkyl, said alkyl or alkenyl group optionally being substituted with halo,
 -OR¹⁰ or -CO₂R¹⁰;

R³ and R⁴ are the same or different and each independently
 represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken
 together represent a saturated or unsaturated C₅-C₇ fused ring to the
 10 benzene ring (Ring III);

R⁵ and R⁶ (y=0) or R⁵, R⁶ and R⁷ (y=1) each independently
 represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally
 being substituted with -OR¹⁰, -SR¹⁰, -S(O)_rR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂,
 -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or one of R⁵, R⁶
 15 and R⁷ can be taken in combination with R⁴⁰ as defined below to
 represent -(CH₂)_r- wherein r is 1 to 4 which can be substituted with lower
 alkyl, lower alkoxy, -CF₃ or aryl, or R⁵ is combined with R⁶ or R⁷ to
 represent =O or =S;

R¹⁰ independently represents H, alkyl, cycloalkyl, cycloalkylalkyl,
 20 heteroaryl, aryl, aralkyl or -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² independently
 represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl,
 heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl,
 cycloalkylalkyl, alkenyl and alkynyl;

R¹¹ represents alkyl or aryl;

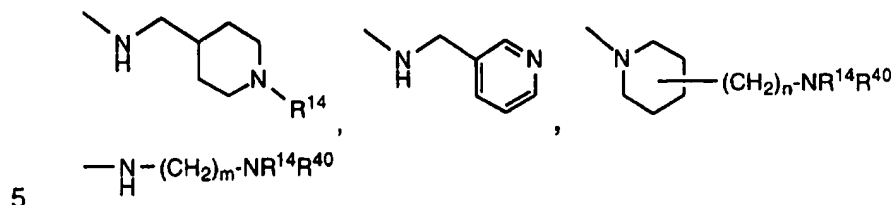
25 the dotted line between carbon atoms 5 and 6 represents an
 optional double bond, such that when a double bond is present, A and B
 independently represent -NO₂, -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or
 -OC(O)R¹⁰, and when no double bond is present between carbon atoms
 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂, H and halo,
 30 dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, oxy, aryl
 and H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4; and

y is 0 (zero) or 1;

n is 0, 1, 2, 3, 4, 5 or 6;

T is -CO-; -SO-; -SO₂-; or -CR³⁰R³¹- wherein R³⁰ and R³¹
 35 independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl,
 heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

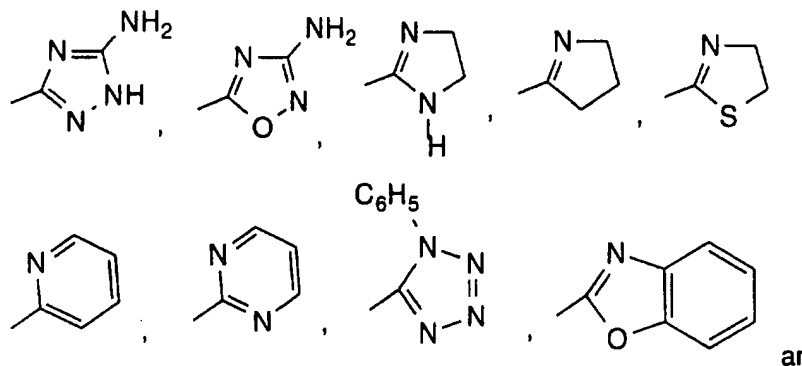
Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR⁴⁰, -SR⁴⁰, -CR⁴⁰R⁴² or -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² are defined hereinbefore



wherein n, R⁴⁰ and R⁴² are defined hereinbefore,

m is 2, 3 4, 5, 6, 7 or 8;

and R¹⁴ represents H, C₁₋₆ alkyl, aralkyl, acyl, carboxamido, cyano,
10 alkoxy carbonyl, aralkyloxy carbonyl, D- and L-amino acids covalently
bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl,
dialkylphosphinyl, N-glycosyl,



15 $\text{-C(NHCH}_3\text{)=CHNO}_2$,
with the proviso that when T is -SO- , Z is not $\text{-NR}^{40}\text{R}^{42}$.

In the compounds of Formula (1.0), preferably a is N and b, c and d are carbon. Preferably A and B each represent H₂ and the optional double bond is absent. Also preferred is that R¹ and R⁴ are H, and R² and R³ are halo, preferably independently Br or Cl. For example, R² is Br and R³ is Cl. These compounds include compounds wherein R² is in the 3-position and R³ is in the 8-position, e.g., 3-Br and 8-Cl.

Also, compounds of Formula (1.0) preferably include compounds wherein R¹ is H, and R², R³ and R⁴ are halo, preferably independently selected from Br or Cl. These compounds include compounds wherein R² is in the 3-position, R³ is in the 7-position and R⁴ is in the 8-position, e.g., 3-Br, 7-Br, 8-Cl. Also included are compounds wherein R² is in the

3-position, R^3 is in the 8-position and R^4 is in the 10-position, e.g. 3-Br, 8-Cl and 10-Br.

Preferably n is zero. Also preferred is that the moiety $-(CH_2)_n-T-Z$ is bonded at the 2-position on the pyrrolidine or azetidine ring. Also preferred is that T is $-CO-$ and Z is $-NR^{40}R^{42}$, more preferably where one of R^{40} or R^{42} is H. Also preferred is that R^{40} is H and R^{42} is 3-pyridylmethyl.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes-- i.e., the Ras gene itself is not activated by mutation to an oncogenic form-- with said inhibition being accomplished by the administration of an effective amount of the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein.

In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

DETAILED DESCRIPTION OF THE INVENTION





The following solvents and reagents are referred to herein by the abbreviations indicated:

tetrahydrofuran (THF);

ethanol (EtOH);
methanol (MeOH);
ethyl acetate (EtOAc);
N,N-dimethylformamide (DMF);
5 trifluoroacetic acid (TFA);
1-hydroxybenzotriazole (HOBT);
1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC);
dimethylsulfoxide (DMSO);
acetic acid (HOAc or AcOH)
10 4-methylmorpholine (NMM);
dimethylaminopyridine (DMAP); and
dimethoxyethane (DME).
t-butoxycarbonyl (BOC)
acetyl(OAc)

15

As used herein, the following terms are used as defined below
unless otherwise indicated:

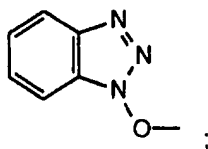
 or  - indicates a pure isomer;
 - when attached to a carbon atom labeled with an asterisk (*),
20 indicates a separated isomer whose stereochemistry is not established;
 - indicates a racemic mixture;

M⁺ -represents the molecular ion of the molecule in the mass
spectrum;

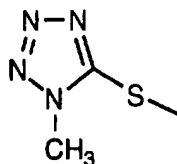
MH⁺ -represents the molecular ion plus hydrogen of the molecule
25 in the mass spectrum;

PMR or NMR refers to proton magnetic resonance spectroscopy
or nuclear magnetic resonance spectroscopy, whose terms are
interchangeable;

Bu-represents butyl;
30 Et-represents ethyl;
Me-represents methyl;
Ph-represents phenyl;
benzotriazol-1-yloxy represents



1-methyl-tetrazol-5-ylthio represents



acyl-a moiety of the formula -COR¹⁵ wherein R¹⁵ represents H, C₁₋₆ alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms (i.e. C₁₋₆ alkyl); for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl and said C₁₋₆ alkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino (-NH₂), alkylamino, cyano (-CN), -CF₃, dialkylamino, hydroxy, oxy (=O), phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -NCOR¹⁰ or -COOR¹⁰.

alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

alkoxycarbonyl - represents a alkoxy moiety, as defined above, covalantly bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -COOCH₃, -COOCH₂CH₃ and -COOC(CH₃)₃;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; wherein said alkenyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂,

-NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂,
-CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms; wherein said alkynyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

amino acid- refers to organic compounds having both an amino group (-NH₂) and a carboxyl group (-COOH). Representative amino acids include glycine, serine, alanine, phenylalanine, tyrosine, S-methyl methionine and histidine;

aryl (including the aryl portion of aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl), wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon and nitrogen atoms in said aryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more aryl groups; wherein said aralkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰; Representative aralkyl groups include benzyl and diphenylmethyl;

aralkyloxy - represents an aralkyl group, as defined above, covalently bonded to an adjacent structural element through an oxygen atom, for example, phenylmethyloxy and phenylethyloxy;

aralkyloxycarbonyl - represents an aralkyloxy group, as defined above, covalantly bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -COOCH₂C₆H₅ and -COOCH₂CH₂C₆H₅;

carboxamido - represents a moiety of the formula -CONH₂ or
 5 -CONR⁴⁰R⁴²;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms; wherein said cycloalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl,
 10 alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

cycloalkylalkyl - represents an alkyl group, as defined above,
 15 wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl groups; wherein said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy,
 20 -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon
 25 atoms interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-; wherein any of the available substitutable carbon and nitrogen atoms in said heteroalkyl chain may be optionally and independently substituted with one, two, three or more of the following: halo, C₁-C₆ alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, -CF₃, -OCF₃, amino,
 30 alkylamino, dialkylamino, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, or -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

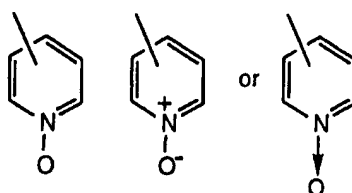
heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic
 35 ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to 14 carbon atoms, wherein said heteroaryl group optionally can be fused with one or more aryl, cycloalkyl, heteroaryl or

heterocycloalkyl rings; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, C₁-C₆ alkyl, aryl, cyano, hydroxy,

- 5 alkoxy, oxy, phenoxy, -CF₃, -OCF₃, amino, alkylamino, dialkylamino, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, or -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰.

Representative heteroaryl groups can include, for example, furanyl, imidazolyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl

- 10 N-oxide wherein pyridyl N-oxide can be represented as:



heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroarylalkyl group may be optionally

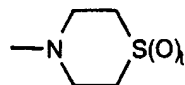
- 15 and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰; as exemplified by 2-, 3- or 4-

- 20 pyridylmethyl or 2-, 3- or 4-pyridylmethyl N-oxide;

heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3

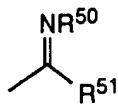
- 25 heteroatoms selected from -O-, -S- and -N-, wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein any of the available substitutable carbon and nitrogen atoms in the ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino,
- 30 hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰

Representative heterocycloalkyl groups can include 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothienyl, 1-, 2-, 3- or 4-piperidyl, 2- or

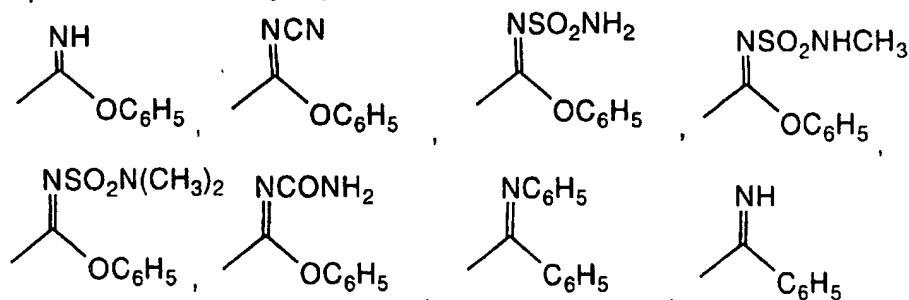


- 3-pyrrolidinyl, 1-, 2- or 3-piperizinyl, 2- or 4-dioxanyl, wherein t is 0, 1 or 2; morpholinyl, heterocycloalkylalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein
- 5 optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy,
- 10 phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

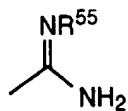
imido - represents a moiety of the formula



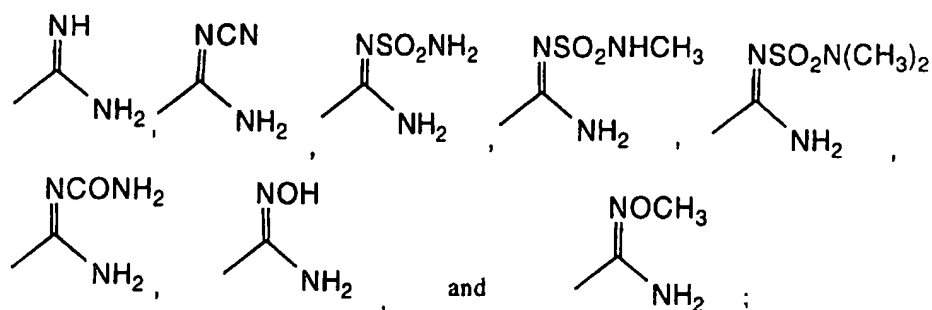
- wherein R⁵⁰ represents H, cyano, aryl, -SO₂NH₂, -SO₂NR⁴⁰R⁴² and carboxamido and R⁵¹ represents aryl and aryloxy.
- 15 Representative imido groups can include, for example,



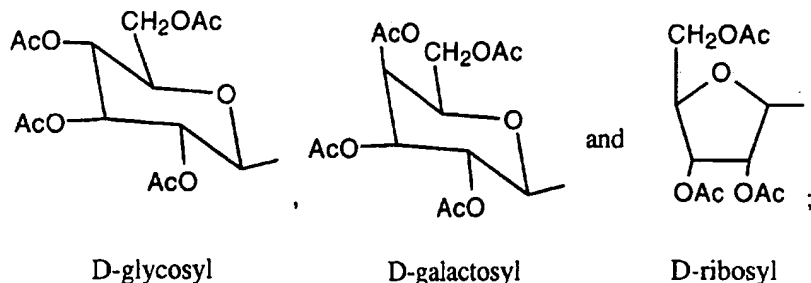
imidamido - represents a moiety of the formula



- wherein R⁵⁵ represents H, cyano, -SO₂NH₂, -SO₂NR⁴⁰R⁴², carboxamido, hydroxy and alkoxy. Representative
- 20 imidamido groups can include, for example,



- N-glycosyl- represents a pyranosyl or furanosyl monosaccharide. Representative N-glycosyl groups include (N \rightarrow 1)-tetra-O-acetyl-D-glucosyl, (N \rightarrow 1)-tetra-O-acetyl-D-galactosyl and (N \rightarrow 1)-tri-O-acetyl-D-ribose, e.g.



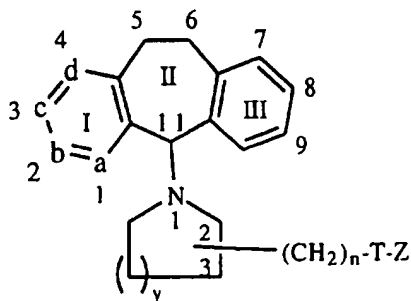
1-amino-2-nitroethenyl represents the formula:
 $-\text{C}(\text{NHCH}_3)=\text{CHNO}_2$;

- dialkylphosphinyl - represents a phosphine (-PO) moiety covalently bonded to two alkyl groups. A representative dialkylphosphinyl group is $-\text{PO}(\text{CH}_3)_2$.

- sulfamoyl - represents a moiety of the formula $-\text{SO}_2\text{R}^{60}$ wherein R^{60} represents amino, alkylamino and dialkylamino. Representative sulfamoyl groups can include, for example, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$.

- sulfonyl - represents a moiety of the formula $-\text{SO}_2\text{R}^{60}$ wherein R^{60} represents alkyl, aryl and arylalkyl. Representative sulfonyl groups can include, for example, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{C}_6\text{H}_5$, $-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$, and $-\text{SO}_2\text{CH}_2\text{C}_6\text{H}_5$.

- Reference to the position of the substituents R^1 , R^2 , R^3 , and R^4 is based on the numbered ring structure:



Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers and diastereoisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures. For example, the carbon atom at the C-11 position can be in the S or R stereoconfiguration. Also, the carbon atom at the C-2 and C-3 positions of the pyrrolidine (y=1) or at the C-2 position of the azetidine moiety (y=0) bonded at C-11 can also be in the S or R stereoconfiguration.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

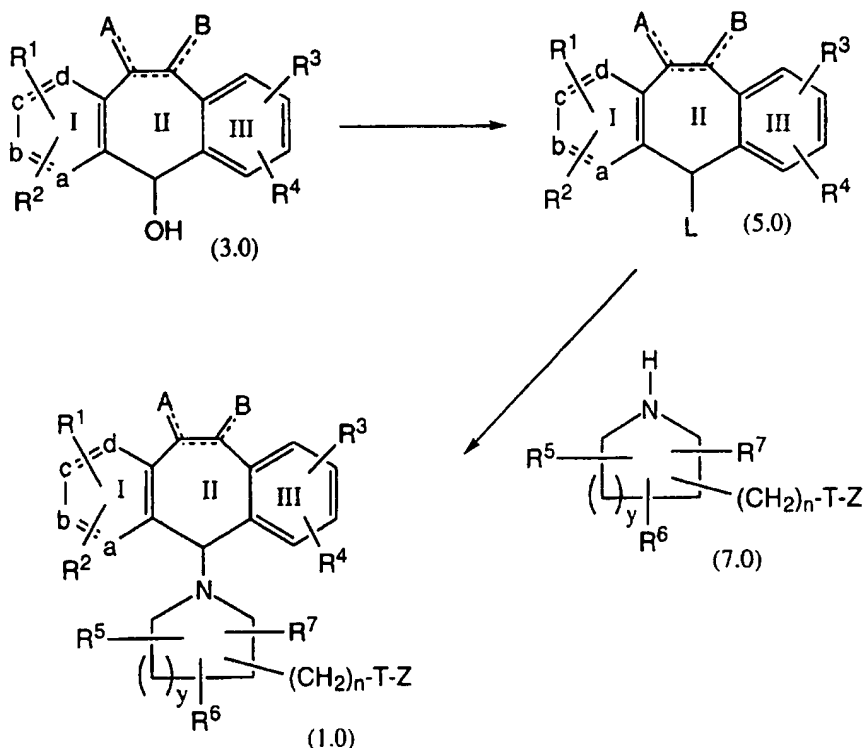
Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in

polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention..

- 5 All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the present invention can be prepared according to the following Scheme 1:

Scheme 1



5

wherein L represents a leaving group such as halo, preferably chloro or a leaving group such as o-tosyl and o-mesyl; the dotted line represents a single or double bond; and a, b, c, d, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, m, n, T and Z are as defined hereinbefore.

- 10 Referring to the Scheme I, compounds of formula (5.0) can be prepared by reacting the compounds of formula (3.0) with a halogenating agent or a sulfonylating agent in the presence of a suitable base, and optional aprotic solvent, in amounts and under conditions effective to give compounds (5.0). Suitable bases include organic bases such as pyridine and triethylamine; or inorganic bases of alkali and alkaline earth metals
- 15 including carbonates such as sodium, lithium, potassium and cesium carbonates, hydroxides such as sodium and potassium hydroxides; hydrides such as sodium or potassium hydride; and sodium t-butoxide, preferably sodium hydride. Suitable aprotic solvents include ethers, DMF,
- 20 DMSO, THF, DME and mixtures thereof, preferably DMF. Preferably the

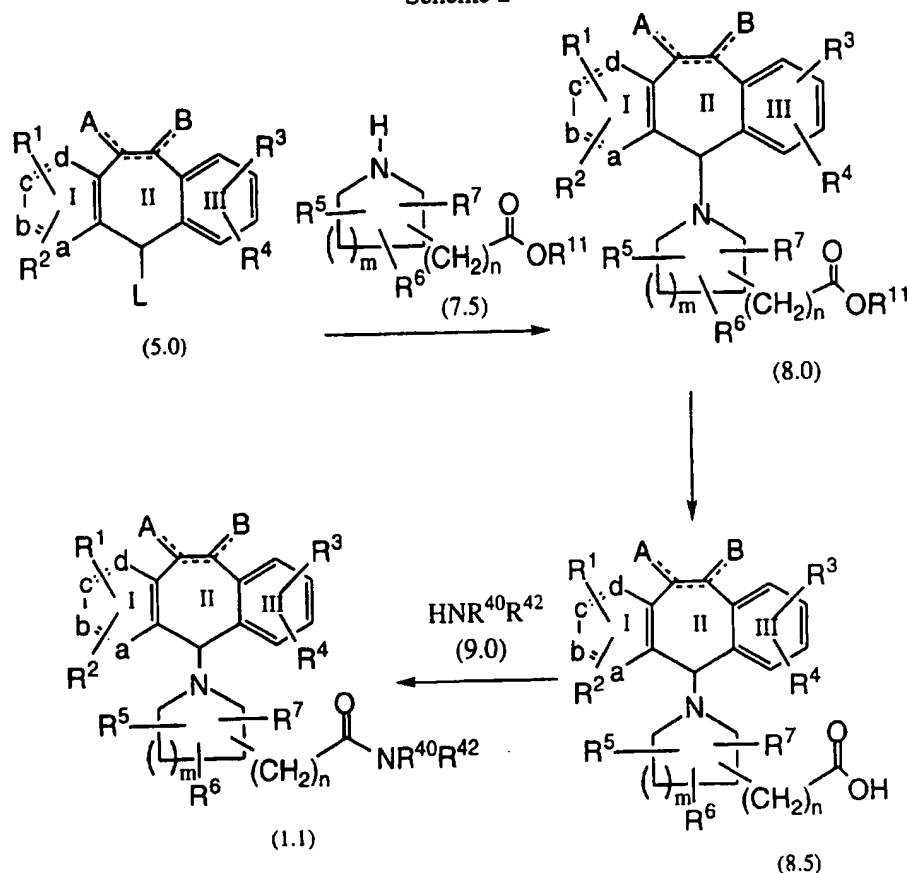
halogenating agent is a chlorinating agent, such as thionyl chloride. The sulfonylating can be sulfonyl chloride, methane sulfonyl chloride or toluene sulfonyl chloride. The amounts of the halogenating agent or the sulfonylating agent can range from about one to about 10 moles per mole
5 of compound (3.0). Temperatures can range from 0° to 50°C, or reflux of the reaction mixture.

The desired tricyclic piperidinyl compounds of formula (1.0) can be prepared by reacting the compounds of formula (5.0) with a suitably substituted pyrrolidine or azetidine compound of formula (7.0) in the
10 presence of a suitable base and optional aprotic solvent, such as those described above, to give compounds (1.0). The amounts of the substituted pyrrolidine or azetidine compound of formula (7.0) to compound (5.0) can range from about one to about 10 moles per mole of compound (5.0). Temperatures can range from about room temperature to
15 about 80°C.

The tricyclic compounds of formula (1.0) can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, evaporation of the organic solvents, followed by chromatography on silica
20 gel or other suitable chromatographic media.

The compound of formula (1.0) wherein T = -CO- and Z = -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² are defined hereinbefore (i.e. an amide) can be prepared in accordance with Scheme 2.

Scheme 2



wherein L represents a leaving group, preferably chloro; the dotted line represents a single or double bond; and a, b, c, d, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹¹, R⁴⁰, R⁴², m and n are as defined hereinbefore.

- 5 Referring to the Scheme 2, compounds of formula (8.0) can be prepared by reacting the compounds of formula (5.0) with a piperdinyl carboxylic acid ester of formula (7.5) in the presence of a base and optional aprotic solvent, in amounts and under conditions effective to give compounds (8.0). Suitable bases and aprotic solvents are described
- 10 hereinbefore. The amounts of compound (7.5) can range from about 1 to about 10 moles per mole of compound (5.0). Temperatures can range from room temperature to about 80°C. Compound (8.0) can be isolated as described hereinbefore.

- Carboxylic acid compounds of formula (8.5) can be prepared by
- 15 hydrolyzing carboxylic acid ester (8.0) with an excess amount of acid or base. Suitable acids include inorganic acids, organic acids or a mixture thereof. Inorganic acids include hydrogen chloride, hydrogen bromide,

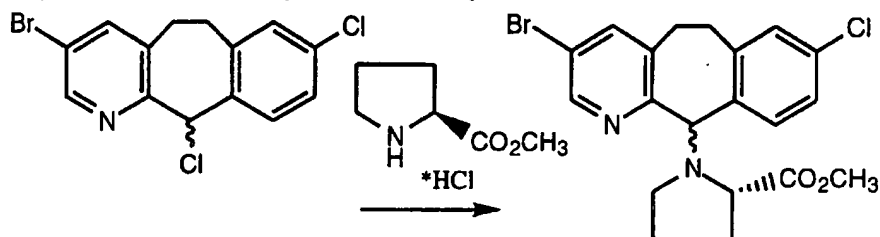
sulfuric acid, nitric acid, phosphoric acid, perchloric acid and the like. Organic acids include acetic, citric, formic, maleic, tartaric, methanesulfonic acid and arylsulfonic acids. Suitable bases, such as sodium hydroxide, or lithium hydroxide in an aqueous alcohol, have been described hereinbefore. The temperature can range from about 0°C to about 100°C.

The desired amide compounds of formula (1.1) can be prepared by reacting the compounds of formula (8.5) with a suitable amine of formula (9.0) in the presence of a base and a suitable aprotic solvent effective to give amide compound (1.1). Suitable bases and aprotic solvents are described hereinbefore. The amounts of amine (9.0) can range from about 1 to about 10 moles per mole of carboxylic acid (8.5). Temperatures can range from 0° to 100°C. Compound (1.1) can be isolated as described hereinbefore.

Compounds of the present invention and preparative starting materials thereof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

Example 1.

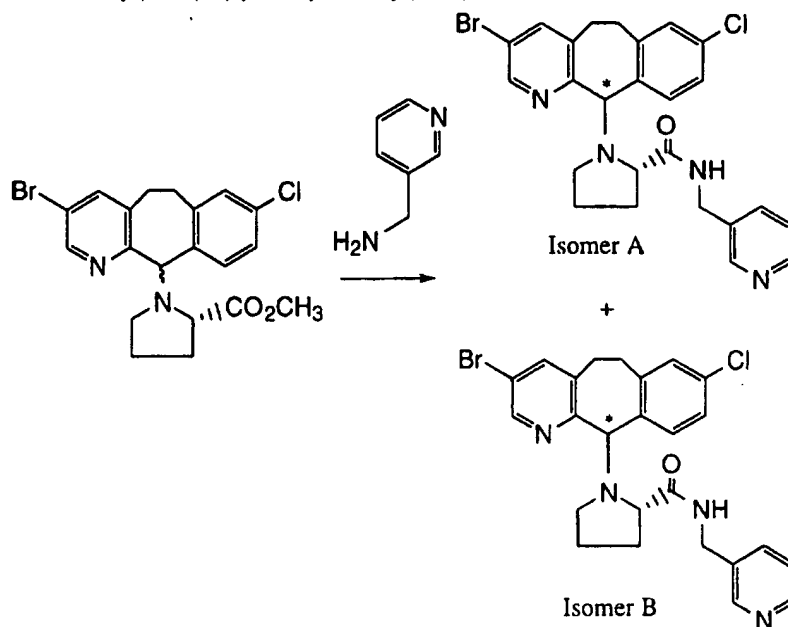
Step A. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-pyrrolidine methyl ester



A mixture of 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.05 g, 3.06 mmole), proline methyl ester hydrochloride (1.52 g 9.18 mmole) and N-methyl morpholine (1.85 g, 18.32 mmole) in DMF (15 mL) is heated at 85°C overnight. The reaction mixture is evaporated to dryness, extracted with CH₂Cl₂ (100 mL), washed with water (2 x 100 mL), the organic extract is dried over MgSO₄ and the solvent evaporated to give an oily residue. The oily residue is flash chromatographed on a silica gel column eluting with hexane-15% ethyl acetate to give 0.78 g of the title compound, a foam. Partial PMR

(CDCl₃, 200 MHz), 8.3 (s, 1H), 7.5 (d, 1H), 7-7.2 (m, 3H), 4.5 (s, 1H), 3.2 (s, 3H).

Step B. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)2-pyrrolidine carboxamide



The title compound of Example 1, Step A (0.43 g, 9.1 mmole) and 3-aminomethylpyridine (0.196 g, 18.12 mmole) are heated at 130°C overnight. The residue is chromatographed on a silica gel column eluting with CH₂Cl₂-3% (CH₃OH-10% conc NH₄OH), and separated to give the title compounds:

Isomer A, 0.062 g, Mass Spec. MH⁺ 513 (FAB); partial PMR (CDCl₃, 200MHz), 8.45 (d, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 7-7.4 (m, 6H), 4.68 (s, 1H) FPT IC₅₀ = 0.059 μM

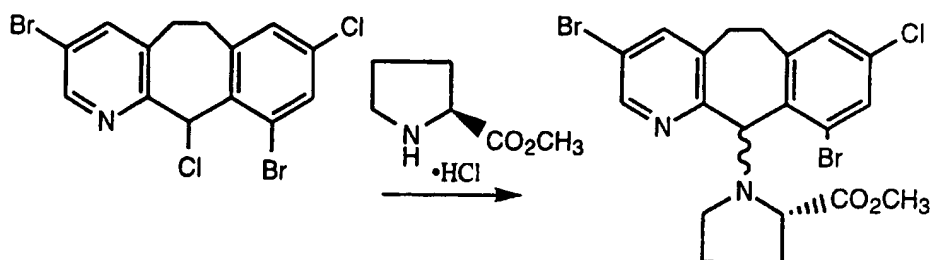
15

Isomer B, 0.042 g, Mass spec. MH⁺513, partial PMR (CDCl₃, 200 MHz), 8.55 (d, 1H), 8.4 (s, 1H), 8.35 (s, 1H), 6.8-7.6 (m, 6H). FPT IC₅₀ = 0.14 μM

Example 2.

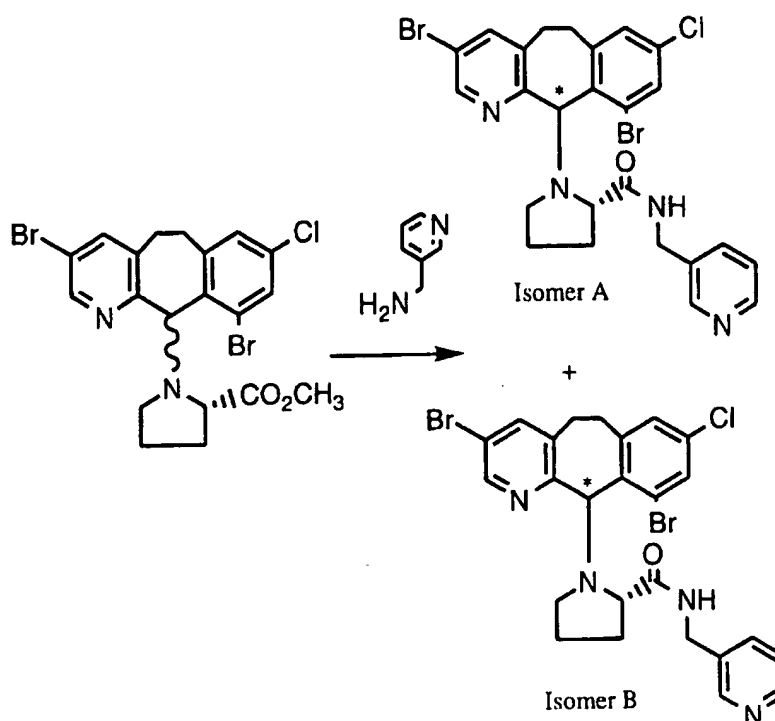
20

Step A. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-pyrrolidine methyl ester



A mixture of 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-
 benzo[5,6]cyclohepta[1,2-b]pyridine (0.5 g, 1.18 mmole) , proline methyl
 ester hydrochloride (0.59 g 3.55 mmole) and N-methyl morpholine (0.72 g,
 5 7.11 mmole) in DMF (10 ML) is heated at 85°C for one hour. The reaction
 mixture is evaporated to dryness, extracted with CH₂Cl₂ (100 mL) and
 washed with water (2 x100 mL). The organic extract is dried over MgSO₄
 and the solvent evaporated, leaving an oily residue which is flash
 chromatographed on a silica gel column eluting with hexane-15% ethyl
 10 acetate to give 0.43 g of the title compound as a foam. Partial PMR
 (CDCl₃, 200 MHz), 8.4 (d, 1H), 7.45 (d, 1H), 7.4 (d, 1H), 7.12 (d, 1H), 5.56
 (s, 1H), 5.01 (m, 1H), 3.55 (m, 1H), 3.23 (s, 3H).

Step B. 1-(3,10-dibromo-8-chloro-6,11-dihydro-5H-
 15 benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)-2-
 pyrrolidine carboxamide



The compound of Example 2, Step A (0.36 g) is dissolved in ethanol (10 mL) and heated at 80 °C with 1N LiOH (aqueous, 4 mL) overnight. The pH is adjusted to 4 with 1N HCl and the solution evaporated to dryness.

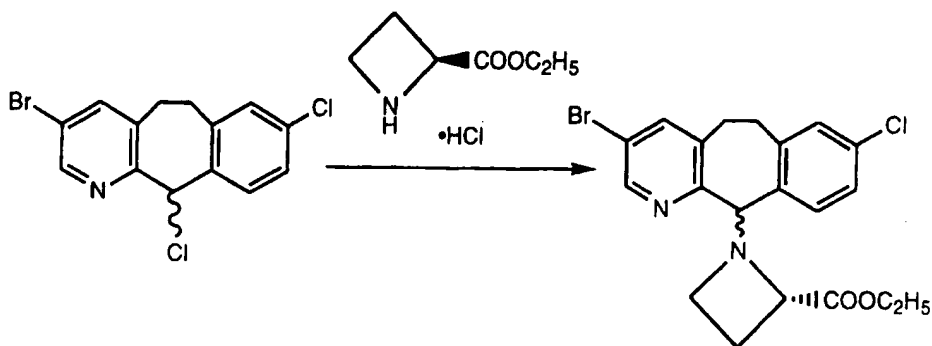
- 5 The product is dissolved in DMF (10 mL) and NMM (0.32 mL), and HOBT (0.187 g), DEC (0.265 g), and 3-amino methyl pyridine (0.16 mL) are added. The reaction mixture is stirred over the weekend, evaporated to dryness, the residue extracted in CH₂Cl₂ (100 mL) and with brine (2 x 100 mL). The organic extract is dried over MgSO₄, evaporated to dryness,
- 10 and chromatographed on a Chiralpak® AD HPLC analytical chiral column (amylose tris(3,5-dimethylphenyl carbamate) coated on a 10 µM silica-gel substrate, trademark of Chiral Technologies, Exton, Pennsylvania), using as the eluting solvent, eluting with 80% hexane/isopropanol (containing 0.25 % diethylamine) to give the title compounds:
- 15 Isomer A (0.124 g) as a foam, Mass Spec. MH⁺ 591 (FAB); partial PMR (CDCl₃, 400MHz), 8.58 (d, 1H), 8.45 (s, 2H), 8.3 (s, 1H), 7.55 (s, 1H), 7.45(m, 2H), 7.28 (m, 2H), 6.82 (s, 1H), 6.81 (t, 1H), 5.72 (s, 1H)
FPT Inhibition: 15% @0.3 µM

- 20 Isomer B, 0.165g, Mass spec. MH⁺591, partial PMR (CDCl₃, 400 MHz), 8.59 (d, 1H), 8.4 (m, 2H), 7.48 (s, 1H), 7.35 (m, 1H), 7.1-7.3 (m, 3H), 6.9 (t, 1H), 5.6 (s, 1H).

FPT IC₅₀ = 0.0052 μ M

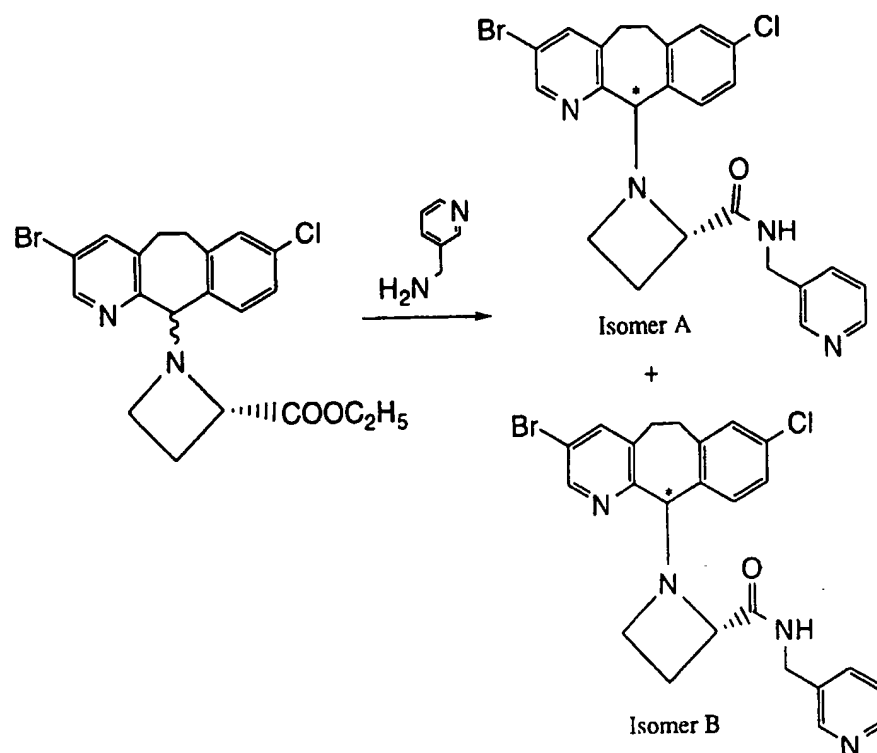
Example 3.

Step A. 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-azetidine methyl ester



A mixture of 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.05 g, 3.06 mmole), azetidine ethyl ester hydrochloride (1.52 g 6.02 mmole) and N-methyl morpholine (1.85 g, 18.32 mmole) in DMF (15 ML) is heated at 85°C overnight. The reaction mixture is evaporated to dryness, extracted with CH₂Cl₂ (100 mL) and washed with water (2 x100 mL). The organic extract is dried over MgSO₄ and the solvent is evaporated to give oily residue which is flash chromatographed on a silica gel column eluting with hexane-15% ethyl acetate, to give 0.72 g of the title compound as a foam. Partial PMR (CDCl₃, 200 MHz), 8.3 (s, 1H), 7.5 (d, 1H), 7-7.2 (m, 3H), 4.5 (s, 1H), 3.2 (s, 3H).

Step B. 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)2-azetidine carboxamide



The compound of Example 3, Step A (0.7 g) is dissolved in ethanol (10 mL) and heated at 80°C with 1N LiOH (aqueous, 3 mL) overnight. The pH is adjusted to 4 with 1N HCl and the solution evaporated to dryness. The product is dissolved in DMF (10 mL) and NMM (0.32 mL), and HOBT (0.187 g), DEC (0.265 g) and 3-aminomethyl pyridine (0.16 mL) are added. The reaction mixture is stirred over the week end at room temperature, evaporated to dryness, and the residue extracted in CH₂Cl₂ (100 mL). The organic extract is washed with brine (2 x 100 mL), dried over MgSO₄, evaporated to dryness and the product is chromatographed on a Chiralpak® AD HPLC analytical chiral column eluting with 80% hexane/isopropanol (containing 0.25 % diethylamine) to give the title compounds:

Isomer A (0.113 g) as a foam, Mass Spec. MH⁺ 499 (FAB); partial PMR (CDCl₃, 400MHz), 8.58 (d, 1H), 8.45 (s, 2H), 8.3 (s, 1H), 7.55 (s, 1H), 7.45(m, 2H), 7.28 (m, 2H), 6.82 (s, 1H), 6.81 (t, 1H), 5.72 (s, 1H)
FPT IC₅₀ = 1.05 μM

Isomer B (0.148g) as a foam, Mass spec. MH⁺499, partial PMR (CDCl₃, 400 MHz), 8.59 (d, 1H), 8.4 (m, 2H), 7.48 (s, 1H), 7.35 (m, 1H), 7.1-7.3 (m, 3H), 6.9 (t, 1H), 5.6 (s, 1H)

FPT Inhibition: 17% @0.1 μ M

PREPARATION OF STARTING MATERIALS

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. The tricyclic compounds (3.0) and substituted piperidinyl compounds (7.0) used as starting materials are known in the art and/or can be prepared using known methods, such as taught in U.S. Patents 5,089,496; 5,151,423; 4,454,143; 4,355,036; PCT /US94/11390 (WO95/10514); PCT/US94/11391 (WO 95/10515); PCT/US94/11392 (WO95/10516); Stanley R. Sandler and Wolf Karo, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., San Diego, California, Vol. 1-3, (1983); in J. March, Advanced Organic Chemistry, Reactions & Mechanisms, and Structure, 3rd Edition, John Wiley & Sons, New York, 1346 pp. (1985); A. J. Boulton and A. McKillop (Eds.), Comprehensive Heterocyclic Chemistry, Volume 7, Four Membered Rings With One Nitrogen Atom, Pergamon Press, Elmsford, New York, (1960-1985); A. J. Boulton and A. McKillop (Eds.), Comprehensive Heterocyclic Chemistry, Volume 4, Part 3, Five Membered Rings With One Nitrogen Atom, Pergamon Press, Elmsford, New York, (1960-1985); J. Am. Chem. Soc. 80, pg. 970 (1958); JOC 33, 3637 (1968); Tetra. Letters, pp. 381-382 (1995); Helvetic. Chem. Acta, 59 (6), pp. 1917-24 (1976); and J. Med. Chem., 33, 71-77 (1990). The starting materials may also be prepared as taught in copending U.S. Application Serial No. 08/410,187 filed March 24, 1995, copending U.S. Application Serial No. 08/577,951 filed December 22, 1995, and copending U.S. Application Serial No. 08/615,760 filed March 13, 1996; the disclosures being incorporated herein by reference. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

For example, the pyrrolidine compounds of formula (7.0), wherein T = -CO- can be prepared by initially preparing a pyrole compound substituted with the requisite 2- or 3-(CH₂)_nCOZ moiety, together any optional -R⁵, -R⁶, -R⁷ and/or -R⁸ moieties, as described in the references cited above and/or other known art. The 2- or 3-substituted pyrole compound can subsequently be reduced using conventional reduction

PAGES 26 - 31

NOT TO BE CONSIDERED FOR INTERNATIONAL PUBLICATION

Pharmaceutical Dosage Form ExamplesEXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

- Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules.
- 5 Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
Total		253	700

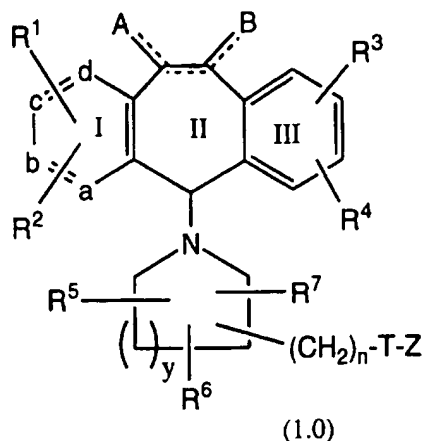
10 Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- 15 While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 5 one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or
- each of a, b, c, and d are independently selected from CR¹ or CR²;
- each R¹ and each R² is independently selected from H, halo, -CF₃,
 10 -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂,
 -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰,
 -NHCO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹,
 -SR¹¹C(O)OR¹¹, -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵ is independently
 15 selected from H and -C(O)OR¹¹, benzotriazol-1-yloxy, tetrazol-5-ylthio, or
 substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl
 group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;
- R³ and R⁴ are the same or different and each independently
 represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken
 together represent a saturated or unsaturated C₅-C₇ fused ring to the
 20 benzene ring (Ring III);
- R⁵ and R⁶ (y=0) or R⁵, R⁶ and R⁷ (y=1) each independently
 represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally
 being substituted with -OR¹⁰, -SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂,
 -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or one of R⁵, R⁶
 25 and R⁷ can be taken in combination with R⁴⁰ as defined below to
 represent -(CH₂)_r wherein r is 1 to 4 which can be substituted with lower
 alkyl, lower alkoxy, -CF₃ or aryl, or R⁵ is combined with R⁶ or R⁷ to
 represent =O or =S;

R^{10} independently represents H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl,

5 cycloalkylalkyl, alkenyl and alkynyl;

R^{11} represents alkyl or aryl;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or

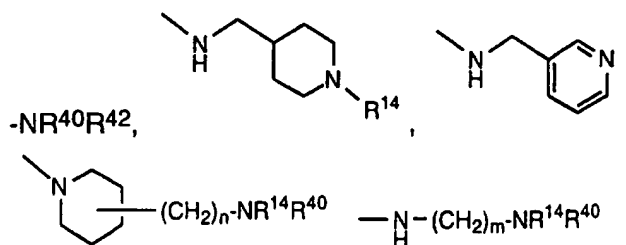
10 $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2 , $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, oxy, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

y is 0 (zero) or 1;

15 n is 0, 1, 2, 3, 4, 5 or 6;

T is $-CO-$; $-SO-$; $-SO_2-$; or $-CR^{30}R^{31}-$ wherein R^{30} and R^{31} independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-OR^{40}$, $-SR^{40}$, $-CR^{40}R^{42}$,

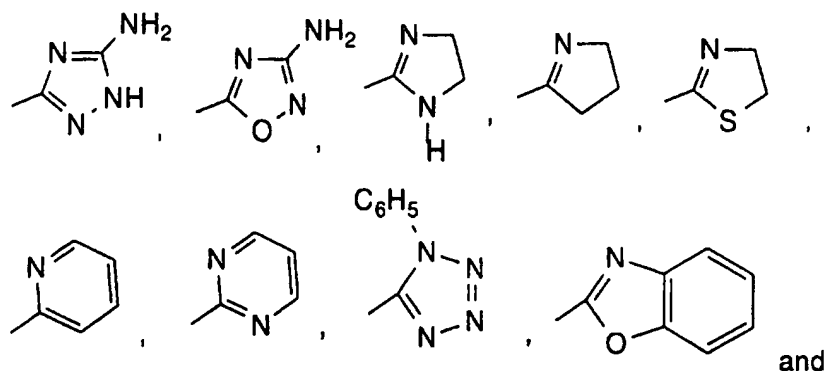
20



wherein n, R^{40} and R^{42} are defined hereinbefore,

m is 2, 3, 4, 5, 6, 7 or 8;

25 and R^{14} represents H, C_{1-6} alkyl, aralkyl, acyl, carboxamido, cyano, alkoxy carbonyl, aralkyloxy carbonyl, D- and L-amino acids covalently bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl,



-C(NHCH₃)=CHNO₂,

with the proviso that when T is -SO-, Z is not -NR⁴⁰R⁴².

5

2. The compound of claim 1 wherein a is N; b, c and d are carbon; A and B each represent H₂ and the optional double bond is absent.

10

3. The compound of claim 2 wherein R¹ and R⁴ are H and R² and R³ are halo selected from chloro and bromo; or R¹ is H and R², R³ and R⁴ are halo selected from chloro and bromo.

15

4. The compound of claim 2 wherein R² is halo in the 3-position and R³ is halo in the 8-position.

5. The compound of claim 2 wherein R² is Br in the 3-position and R³ is Cl in the 8-position.

20

6. The compound of claim 2 wherein R¹ is H and R², R³ and R⁴ are halo selected from chloro and bromo.

7. The compound of claim 2 wherein R² is halo in the 3-position, R³ is halo in the 8-position and R⁴ is halo in the 10-position.

25

8. The compound of claim 2 wherein R² is bromo in the 3-position, R³ is chloro in the 8-position and R⁴ is bromo in the 10-position.

30

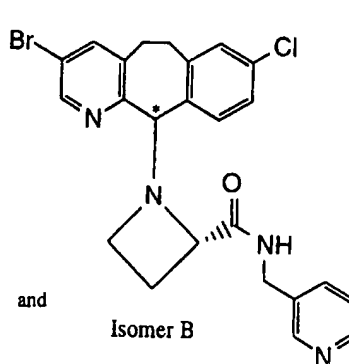
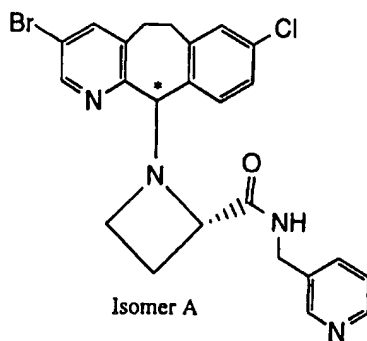
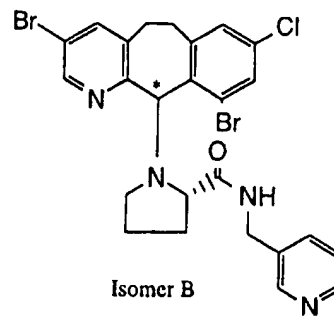
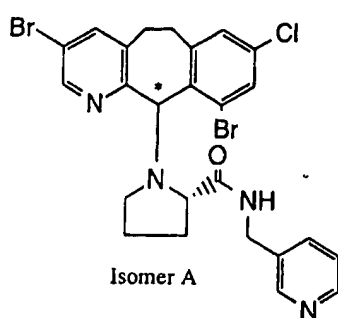
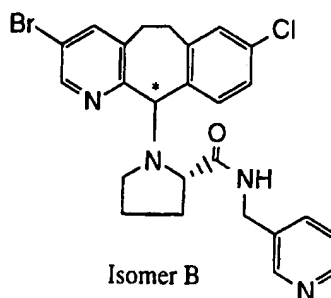
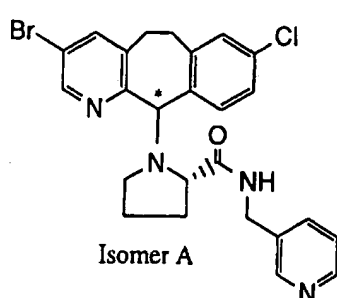
9. The compound of claim 3 wherein the moiety $-(CH_2)_n-T-Z$ is bonded at the 2-position on the pyrrolidine ($y=1$) or azetidine ($y=0$) ring.

10. The compound of claim 9 wherein n is zero; T is $-CO-$ and Z is
5 $-NR^{40}R^{42}$.

11. The compound of claim 10 wherein R^{40} is H; and R^{42} is 3-pyridylmethyl.

10 12. The compound of claim 1 selected from any of Examples 1-3.

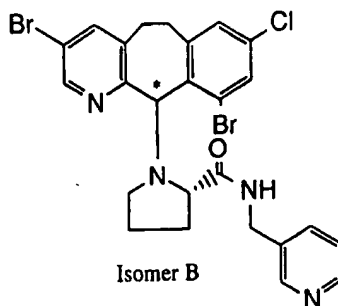
13. The compound of claim 12 which is selected from



and

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 which is



15. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

16. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.

17. The method of claim 16 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

18. The method of claim 16 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

19. The method of claim 16 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

20. The method of claim 16 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/15902

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 A61K31/435 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 396 083 A (SCHERING CORP) 7 November 1990 see claims ---	1,15-20
A	WO 92 00293 A (SCHERING CORP) 9 January 1992 see claims ---	1,15-20
A	WO 95 10515 A (SCHERING CORP) 20 April 1995 see claims ---	1,15-20
A	WO 95 10516 A (SCHERING CORP) 20 April 1995 see claims ---	1,15-20
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

24 November 1997

Date of mailing of the international search report

02.12.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/15902

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GB 1 593 417 A (SQUIBB & SONS INC) 15 July 1981 see page 20, line 15 - page 22, line 5; claims; examples 73-94 -----</p>	1,15-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/15902

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 16-20
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 97/15902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0396083 A	07-11-90	US 5089496 A	18-02-92
		AT 114650 T	15-12-94
		AU 643946 B	02-12-93
		AU 5642090 A	29-11-90
		CA 2053903 A	02-11-90
		DE 69014393 D	12-01-95
		DE 69014393 T	01-06-95
		EP 0471750 A	26-02-92
		ES 2064520 T	01-02-95
		IE 66392 B	27-12-95
		IL 94258 A	07-10-94
		JP 4504724 T	20-08-92
		KR 9509859 B	29-08-95
		NO 179674 B	19-08-96
		OA 9521 A	15-11-92
		WO 9013548 A	15-11-90
		US 5151423 A	29-09-92
		US 5438062 A	01-08-95
WO 9200293 A	09-01-92	AT 126226 T	15-08-95
		AU 646878 B	10-03-94
		AU 8225291 A	23-01-92
		CA 2085878 A	23-12-91
		DE 69112061 D	14-09-95
		DE 69112061 T	14-12-95
		EP 0535152 A	07-04-93
		ES 2096657 T	16-03-97
		HK 186496 A	11-10-96
		IE 68935 B	24-07-96
		IL 98572 A	31-07-95
		JP 7061998 B	05-07-95
		KR 9612368 B	20-09-96
		US 5422351 A	06-06-95
WO 9510515 A	20-04-95	AU 7930994 A	04-05-95
		CA 2174105 A	20-04-95
		EP 0723538 A	31-07-96
		HU 76066 A	30-06-97
		JP 8510759 T	12-11-96
		ZA 9407970 A	12-07-96

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 97/15902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9510516 A	20-04-95	AU 7970394 A	04-05-95
		CA 2174104 A	20-04-95
		EP 0723540 A	31-07-96
		HU 76056 A	30-06-97
		JP 8510760 T	12-11-96
		ZA 9407971 A	12-07-96

GB 1593417 A	15-07-81	US 4062858 A	13-12-77
		US 4111940 A	05-09-78
		CA 1094556 A	27-01-81
		DE 2757503 A	29-06-78
		FR 2375231 A	21-07-78
		JP 53087399 A	01-08-78
		US 4128717 A	05-12-78
		CA 1105020 A	14-07-81
		US 4179564 A	18-12-79
